

AAV and Eye-Directed Gene Therapy – Luk Vandenberghe, Ph.D.

The eye is an attractive target for gene therapy for acquired, progressive and inherited diseases of the retina. The relative ease of access, the limited projected vector dose, the minimal anticipated immunological sequelae and vector spread are factors that likely will positively impact on the feasibility and safety of such therapies. Several preclinical strategies tackling retinal disease are therefore evolving to the clinic.

Our laboratory has focused on the pre-clinical development of AAV and lentiviral vectors in the eye^(1, 8). Many variables determine the profile of an optimal gene transfer vehicle, many of which are known to be imposed by vector. Cellular specificity of transduction in the eye, gene transfer efficiency and various safety aspects can be modulated by altering the gene transfer vehicle. In the recent years, our laboratory has developed several novel variants of lentiviral⁽⁴⁾, adenoviral⁽⁷⁾ and adeno-associated viral⁽⁹⁾ vectors. Much like candidate selection strategies in small drug development, one can consider each of these original vector systems as a lead for further optimization specific for the therapeutic aim. The libraries of these natural and engineered variants serve as a combinatorial set used to determinate and select the safest and most efficient vector. Subsequent structure-function analysis on these data may then lead to the further tailoring of the vector to a particular therapeutic need.

By selecting the optimal route of injection together with the serotypes used, vector technology enables transgene expression in most retinal cell types in small and large animal models^(2, 8). In combination with advances in tissue specific promoters and pharmacological regulation of expression, the use of vectors for target validation, reverse genetics or disease modeling in the eye^(3, 5, 6)

(PETER – CSHL PICTURE)

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